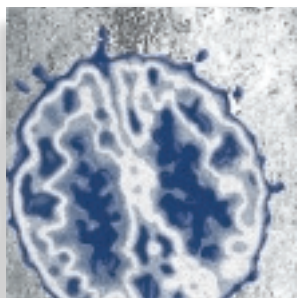


## Melatonin in animal models

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*Melatonin is a hormone synthesized and secreted during the night by the pineal gland. Its production is mainly driven by the circadian clock, which, in mammals, is situated in the suprachiasmatic nucleus of the hypothalamus. The melatonin production and release displays characteristic daily (nocturnal) and seasonal patterns (changes in duration proportional to the length of the night) of secretion. These rhythms in circulating melatonin are strong synchronizers for the expression of numerous physiological processes. In mammals, the role of melatonin in the control of seasonality is well documented, and the sites and mechanisms of action involved are beginning to be identified. The exact role of the hormone in the diurnal (circadian) timing system remains to be determined. However, exogenous melatonin has been shown to affect the circadian clock. The molecular and cellular mechanisms involved in this well-characterized "chronobiotic" effect have also begun to be characterized. The circadian clock itself appears to be an important site for the entrainment effect of melatonin and the presence of melatonin receptors appears to be a prerequisite. A better understanding of such "chronobiotic" effects of melatonin will allow clarification of the role of endogenous melatonin in circadian organization.*

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The Earth's rotation on its axis, the orbit of the Earth around the Sun, and the orbit of the Moon around the Earth induce rhythmic geophysical phenomena. Organisms are thus affected by daily and seasonal variations of many physical factors of their environment. The ability to adapt to this changing environment is an essential survival mechanism. As a result, life has evolved to adapt to periodically changing environmental demands, and to anticipate them according to their predictability. Circadian and seasonal rhythms in biochemical, metabolic, endocrine, physiological, and behavioral processes are a fundamental feature of all living organisms, reflecting the need to ensure that biological functions occur at a given time of the day or year. The most obvious example is the fact that many animals are active only during the light period (diurnal species; human belong to this group) or in the dark period (nocturnal species), and are inactive during the other part of the day (sleep/wake cycle). Other rhythms, such as reproduction, diapause, hibernation, fur color changes, and migration, can also be given as examples. Precise timing is required at all levels from behavior to gene expression, and its dysregulation causes malfunction.

Since the beginning of time, mankind has been fascinated by the sun and the invariably changing seasons, and ancient medical scripts include considerations on the variation of disease through the seasons. Disorders of rhythmicity are characteristic of—and may underlie—a variety

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## Selected abbreviations and acronyms

<b>DMH</b>	<i>dorsomedial hypothalamus</i>
<b>LD</b>	<i>light/dark</i>
<b>LH</b>	<i>luteinizing hormone</i>
<b>PT</b>	<i>pars tuberalis</i>
<b>SCN</b>	<i>suprachiasmatic nucleus</i>
<b>SP</b>	<i>short photoperiod</i>

of medical and behavioral disorders. For example, sleep and circadian rhythms are often disrupted in neurological disorders and there is increasing evidence that alterations in the sleep/wake cycle accompany many types of neurological disorders. Moreover, in our modern human society, there is an increasing incidence of “circadian misalignment” caused by behaviors that perturb the relationship between light-mediated and activity-related input to the circadian system (eg, delayed resynchronization to local time [jet lag] or shift work rotation associated with general malaise [especially insomnia] and decrements in work productivity and increases in accidents).<sup>1</sup> Additionally, in our aging society, there is a high incidence of circadian disorders, particularly disturbed sleep patterns, which reduce the quality of life. Moreover clinical responses to drug therapies, including those for cancer,<sup>2</sup> can crucially depend on the state of the patient’s circadian system.

The challenge for scientists is to understand the functional mechanisms involved and develop strategies to control or treat these disorders, which have important economic and health consequences.

The functional mechanism used for the daily or seasonal organization of functions is far from well understood. We now know that, in mammals, these adaptive processes are organized within a circadian network comprising an endogenous self-sustained oscillator, synchronizing clock inputs, and various clock outputs. The major circadian oscillator is located in the suprachiasmatic nuclei (SCN) of the hypothalamus and the decoding of its genetic background is underway. Photic and nonphotic inputs act directly or indirectly on the rhythms of clock gene expression to synchronize the circadian oscillations to exactly 24 h.<sup>3</sup> The most efficient synchronizer is the daily light/dark (LD) cycle, but other factors, such as food restriction, locomotor activity, and chronobiotic drugs, are well-defined clock synchronizers as well.<sup>4</sup> The circadian oscillator outputs allow the internal synchronization and temporal organization of physiological, endocrine, and behavioral functions. From the hypothalamic clock, various efferent pathways have been described, one of

the most important reaching the pineal gland. This endocrine structure synthesizes and releases melatonin.\* Melatonin is synthesized and secreted during the dark period of the LD cycle, independent of whether the animal is diurnally or nocturnally active, and the duration of the nocturnal production is proportional to the length of the night.<sup>8,9</sup> Melatonin is thus an important efferent hormonal signal from the clock and its pattern of secretion provides both a daily and seasonal endocrine message to any structure or organ that can “read” it. It is now well established, as will be discussed below, that these messages are directly involved in the regulation of both circadian and seasonal rhythms in mammals.

Before we start the description of current knowledge, it should be mentioned that, at high doses, exogenously administered melatonin has been reported to be a potent free radical scavenger.<sup>10,11</sup> This effect can be explained through direct scavenging of free radicals or through interactions of enzyme that improve total antioxidative defense capacity. Even though the physiological nature of such an effect could be questioned, it should not be neglected when assessing the therapeutic potential of the hormone,<sup>12</sup> especially because the binding of melatonin to quinone reductase (QR2), an enzyme with well-known oxidoreductive properties, has recently been demonstrated.<sup>13</sup>

## Melatonin and seasonal function

The duration of the peak of melatonin secretion is positively correlated with the length of the night period. Experimentally, it has been demonstrated that the brain is able to integrate photoperiodic information through these changes in duration of melatonin synthesis. This explains the current use of this hormone in farming to control seasonal functions (eg, fur growth, reproduction, and milk production). This also opens therapeutic perspectives if we consider the hypothesis of Wehr<sup>14</sup> that “the photoperiod-induced changes in the duration of melatonin secretion drive the annual cycle that occurs in

\*Although the pineal gland is the major source of melatonin, other sources do exist. The retina is one such extrapineal source.<sup>5,6</sup> However, and contrary to what happens in some nonmammalian vertebrates, mammalian retinal melatonin does not contribute to circulating melatonin. The Harderian and lachrymal glands, gastrointestinal tract, red blood cells, platelets, and mononuclear cells have also been identified as sites of melatonin synthesis. Melatonin does not appear to be released into the general circulation from these tissues, at least under normal physiological conditions.<sup>7</sup> Moreover, the synthesis of melatonin in these tissues does not appear to be rhythmic.

seasonal affective disorders.” The exact mechanism of action of melatonin is unclear. The duration of nocturnal melatonin production is the key signal,<sup>8</sup> but the existence within this signal of a melatonin-driven circadian rhythm of sensitivity to melatonin has been proposed to explain the photoperiodic response.<sup>15</sup> In fact, our understanding of melatonin’s physiological functions depends on the understanding of how and where its action is exerted. Considering the lipophilic nature of the hormone, interactions with specific intracellular proteins<sup>16,17</sup> or nuclear receptors cannot be excluded; however, melatonin seems to exert its effects principally throughout high-affinity G-protein-coupled receptors. The introduction of 2-[<sup>125</sup>I]iodomelatonin (<sup>125</sup>I-Mel)<sup>18</sup> heralded the development of the melatonin receptor field. The cloning of the first high-affinity melatonin receptor in 1994 by Ebisawa et al<sup>19</sup> then led to the subsequent identification of three types of vertebrate melatonin receptors (MT1, MT2, and Mel<sub>1c</sub>), and this very probably is only the beginning of a long list. Considering the photoperiodic responses, the melatonin receptors involved most probably are of the MT1 subtype. Indeed, the gene of the only other melatonin receptor subtype found in mammals, MT2, is non-functional in two highly photoperiodic species, Siberian and Syrian hamsters (Weaver and Reppert, unpublished data cited in reference 20). The target sites mediating melatonin control of photoperiod-dependent seasonal functions and especially the annual sexual cycle have not yet been totally determined. Contrary to what is generally claimed, melatonin receptors are present in a large number of structures in mammals (more than 110 brain structures have been identified, among them the internal granular layer and the external plexiform layer of the olfactory bulb, lateral septum, septohippocampal nucleus, caudate putamen, bed nucleus of the stria terminalis, SCN, mediobasal hypothalamic nuclei, paraventricular nuclei of the hypothalamus, paraventricular nuclei of the thalamus, intergeniculate leaflet, central and medial amygdaloid nucleus, inferior colliculus, fasciculus retroflexus, substantia nigra, and frontal, orbitofrontal and parietal cortex; numerous peripheral organs also contain melatonin receptors<sup>21-25</sup>). However, a great variability has been noted in the number and location of structures among the species, as well as large differences in receptor density between structures and in the same structures between species. Few structures are common, even among species from the same family,<sup>21</sup> and very probably this should be correlated to either the numer-

ous photoperiodic responses, which are different from one species to another, or the many different effects described for melatonin.

One structure, however, the pars tuberalis (PT) of the pituitary, which contains a very high density of melatonin receptors in all mammals studied, is thought to be of primary importance in photoperiodic response. Its density of melatonin receptors exhibits clear seasonal changes in photoperiodic species, but not in nonphotoperiodic mammals,<sup>26,27</sup> and its implication in the control of seasonal secretion of prolactin has been demonstrated.<sup>28-31</sup> The PT is thus a good model to delineate the melatonin’s signal transduction pathways<sup>32,33</sup> and to study how the cellular response can distinguish between long- and short-duration melatonin signals.

The cyclic adenosine monophosphate (cAMP)-mediated pathways appear to be central to the melatonin readout. Pretreatment with melatonin has been demonstrated to induce a sensitization of adenylate cyclase, and a potentiated cAMP response to forskolin stimulation.<sup>34,35</sup> Melatonin pretreatment that is effective in potentiating cAMP accumulation in the PT is duration-dependent (between 0-16 h) and corresponds well with the duration of the nocturnal melatonin signal.<sup>34</sup> The nocturnal melatonin signal is also crucial for the rhythmic expression in the PT of several cAMP-responsive genes, including the transcriptional inhibitor-inducible cAMP early repressor (ICER), and of several clock genes.<sup>36,37</sup> Indeed, two components of the molecular clock, namely *Per1* and *Cry1*, are rhythmically expressed in the PT. Furthermore, other components of the clock like *Timeless*, *Clock*, and *Per2* (Pévet P et al, unpublished observations) are also expressed in the PT, at least in the PT of some rodents, raising the possibility that the PT might contain a complete set of clock genes.<sup>33,36,38-41</sup> However, the clock gene expression in the PT differs from what is observed in the SCN or other peripheral tissues (peripheral oscillators) because it appears to be directly driven by melatonin. Removal of the pineal gland abolishes rhythmic PT gene expression, and extension of the dark phase of the LD cycle dampens the amplitude of the *Per1* in PT cells.<sup>39</sup> *Cry1* is rapidly and very strongly induced by melatonin administration. In nontreated animals, a peak of expression occurs during the dark phase (ie, at a time when melatonin is present in the bloodstream). This indicates that melatonin may gate the expression of *Cry1* in the PT, suggesting that these clock genes are involved in the melatonin readout mechanism. *Cry1* expression appears

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to be anchored to the onset of melatonin secretion. It acts as a sensor of melatonin onset, rather than a marker of the duration of the melatonin signal.

*Per1* mRNA peaks early in the day, when blood plasma melatonin levels are back to low levels. *Per1* expression thus appears to be linked to the offset of melatonin secretion. This dual effect of melatonin together with its photoperiod-dependent pattern in plasma levels may provide the basis of a time measurement mechanism. This model may help understand how the PT is involved in the seasonal control of prolactin secretion by the PT. The validation of such a model will, however, require further experiments and the complete understanding of the melatonin and photoperiodic readout requires a link with identified downstream response in the PT. This is still difficult. It is through the production of a prolactin-releasing (or release inhibitor) factor that the photoperiodic and melatonin information to lactotroph cells in the pituitary are relayed. This factor, termed “tuberalin,”<sup>30,42</sup> has not yet been identified.

Photoperiod-induced changes in prolactin secretion, however, are not enough to explain the seasonal sexual cycle. This implies that in order to mediate photoperiodic information melatonin must act on other target sites. This view is supported by the fact that Syrian hamsters bearing lesions to the dorsomedial hypothalamus (DMH) and infused with melatonin to mimic short photoperiod (SP), display differential responses in terms of prolactin and luteinizing hormone (LH).<sup>43</sup> While the prolactin response remains intact, the LH response is blocked by the DMH lesion.<sup>43</sup> Moreover, in sheep, melatonin implants in the mediobasal hypothalamus block the effects of SP on LH but not on prolactin, while implants close to the PT inhibit prolactin secretion.<sup>44</sup> Interestingly, melatonin binding sites have been detected in the DMH in the Syrian hamster, although with a very low density, and their density depends on the photoperiod (Pévet P et al, unpublished data).

The hypothesis of a parallel and concomitant action of melatonin on different structures to transduce the photoperiodic message is attractive. The photoperiod is known, through changes in duration of melatonin secretion, to control not only the reproductive annual cycle, but also a large number of other seasonal functions (eg, body weight, hibernation, daily torpor, fur color changes, and migration). Furthermore, not all seasonal functions are expressed in every species and different control mechanisms may be involved. For example, SP induces an acti-

vation of the sexual axis in sheep, but inhibition in Syrian and Siberian hamsters; and hibernation in the Syrian hamster is directly dependent on photoperiod, while in the European hamster it is dependent on a “circannual clock” entrained by photoperiod. It thus seems likely that melatonin acts at different structures according to the species and the function. This concept would account for the large interspecies differences observed in mammals in the distribution of structures containing melatonin receptors. Interestingly, and in support of this concept, a pharmacological dissociation of photoperiodic-controlled seasonal functions has been reported. S 22153, a melatonin antagonist of MT1 and MT2 melatonin receptor subtypes, caused a decrease in the duration of hibernation in Syrian hamsters under SP and low temperature, but did not affect SP-induced gonadal atrophy.<sup>45</sup>

## Melatonin and circadian function

In most nonmammalian vertebrates, the rhythmic synthesis and secretion of melatonin is the direct output of circadian clock, and the rhythmic changes in the concentration of circulating melatonin are fundamental to circadian rhythmicity.<sup>46</sup> In mammals, despite the presence of melatonin receptors in the SCN of most species indicating hormonal feedback on the clock, the consensus has been that melatonin has only a limited role in circadian organization. This view has arisen, in part, since pinealectomy has little effect on circadian organization.<sup>47</sup> Melatonin rhythm, however, is only one of the outputs of the clock and it is probable that, for the organization of circadian activities, a number of different output signals from the clock are involved in the distribution of circadian information to target tissues.<sup>48,49</sup> This does not preclude an important role for melatonin in circadian organization.<sup>36</sup> After pinealectomy, for example, subtle desynchrony of several physiological functions has been described,<sup>50</sup> and the reentrainment of the rat locomotor activity rhythm is modified after a phase shift of the LD cycle.<sup>51</sup> One week after pinealectomy, the firing rate rhythm of SCN neurons in vitro is altered, as well as the daily rhythm of responsiveness to melatonin.<sup>52</sup> It is also known that melatonin interferes with metabolic activity (glucose utilization and protein synthesis) in the SCN.<sup>53</sup> The SCN may use the daily melatonin signal to convey the circadian message to any system that can “read” it, ie, to any structure or organ possessing melatonin receptors, either in the central nervous system or at the periphery.<sup>9,54</sup>



This concept helps explain numerous results in the literature: the melatonin inhibition of spontaneous and light evoked activity of cells in the intergeniculate leaflet<sup>55</sup>; melatonin-enhancing splenic lymphocyte proliferation<sup>56,57</sup>; melatonin-induced inhibition of leukocyte rolling and adhesion to rat microcirculation<sup>58</sup>; melatonin-induced vasoconstriction of cerebral and tail arteries<sup>59</sup>; and melatonin regulation of emotional behavior.<sup>60</sup>

What could be the mechanism involved? Clock genes are expressed widely in mammalian tissues. It appears that cyclical expression of these genes in the periphery is driven by the SCN. The role of melatonin in regulating rhythmic clock gene expression in peripheral tissues as described in the PT (see above) may be one of the mechanisms for tissue-specific regulation of the phase of rhythmicity. Interestingly, it has been demonstrated that the circadian rhythm of melatonin receptor density in rat PT is suppressed after pinealectomy and melatonin drives this rhythm directly.<sup>61,62</sup> Even if the role of endogenous melatonin on clock functioning is not yet defined, the presence of melatonin receptors within the SCN indicates that exogenous melatonin affects circadian regulation, which is of potential therapeutic value.

### Exogenous melatonin and circadian rhythms

Exogenous melatonin is known to be able to influence, directly or indirectly, the phase and/or the period of the circadian clock. In terms of treatments, this means that exogenous melatonin (or any agonist) can be used as a pharmacological tool to manipulate sleep-wake cycle and other circadian rhythms (chronobiotic properties<sup>63</sup>). It has long been known that administration of melatonin can entrain free-running activity rhythms in rodents.<sup>20,64</sup> Entrainment means that the period of the observed rhythm must adjust to, and equal, the synchronizer (zeitgeber) cycle (T), and a stable phase relation must be established between the rhythm and the zeitgeber cycle. This synchronization process occurs through daily phase shifts. Administering melatonin for a series of T values, 24 h, 23 h 50 min, 23 h 45 min, 23 h 35 min, and 23 h 25 min<sup>65</sup> has led to the definition of the limiting phase advance value to which the rat activity rhythm entrains to melatonin at 35 min. The entrainment limits found in this study correspond quite well to the maximum daily phase shift values defined by the melatonin phase response curve,<sup>66</sup> and the magnitude of phase shift responses to a single melatonin injection<sup>67</sup> (range 15-52

min). Daily acute melatonin administration in the rat thus causes “true” entrainment as defined by Enright et al.<sup>68</sup>

Interestingly, when melatonin is administered by daily infusion, the phase angle difference between the entrained rhythm and the zeitgeber (melatonin) depends upon the duration of the infusion period. A negative phase angle is observed and its value increases with the duration of the infusion period.<sup>69</sup> Moreover, with long infusion times (8 h and, more especially, with 16 h), melatonin induces a change in the free-running period in the first days, suggesting that melatonin delays the pacemaker each day until entrainment occurs. In other words, with a long duration of infusion, entrainment occurs earlier than predicted by the model based on acute melatonin administration. The magnitude of the change in period increases significantly with the duration of infusion. These observations suggest that, beside its chronobiotic properties, melatonin affects the circadian clock properties (effect on the period  $\tau$ ?). This conclusion is supported by the results obtained after a “skeleton” infusion. Under these conditions, melatonin induced entrainment after a time during which circadian periods were either lengthened (in a fraction of the animals) or shortened (in the others).<sup>69</sup> This finding suggests that, to achieve entrainment, melatonin has to induce either a phase delay (when the period is shortened) or a phase advance (when the period is lengthened). Such a dual effect of melatonin has also been reported in other studies. For example, when rats received a 5 h phase advance of the dark onset in LD conditions, those injected melatonin daily at the new dark onset reentrained with decreased latency; some of the animals did so by phase delays, whereas others did so by phase advances.<sup>66</sup> Melatonin has been reported to entrain hamsters and *Arvicanthis ansorgei*, a diurnal rodent, by inducing phase advances when the free-running period is longer than 24 h and phase delays when the period is shorter than 24 h.<sup>70-72</sup> All these observations strongly suggest that the effects of exogenous melatonin are complex and depend on the period before entrainment.

Another potential effect of exogenous melatonin should be considered. A single application of melatonin within the SCN, in vivo, induced a long-lasting increase in the amplitude of the nocturnal melatonin secretion.<sup>73</sup> This effect demonstrates that exogenous melatonin is able to sustain the oscillation of the clock and suggests a possible role for endogenous melatonin in mammals.

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## Sites of action for the effects of exogenous melatonin on the circadian activities

In the experiments reported above, responsiveness to melatonin is restricted to a narrow window of sensitivity, which is generally late in the subjective afternoon, but depends upon the duration of the melatonin signal as well as the previous free-running period. The finding that pinealectomized rats entrain to daily melatonin administration<sup>67,69</sup> indicates that endogenous melatonin is not necessary for the entrainment effect of exogenous melatonin, for example, by entraining a window of sensitivity to melatonin.<sup>15</sup> Nocturnal melatonin production is a direct output of the SCN circadian clock. Exogenous melatonin is effective at a time when endogenous melatonin is not produced. Consequently, the effects of melatonin administration *in vivo* appear not to be related to the role of endogenous melatonin on circadian function. This conclusion is reinforced by the observation that to obtain entrainment of the circadian activity rhythm of rodents kept under constant darkness (DD), high doses of melatonin have to be used, independently of the mode of administration.<sup>69,74,75</sup> These doses of melatonin produce peak serum levels 100- to 1000-fold higher than the endogenous melatonin nighttime levels. The necessity of such a high dose of melatonin is unlikely to be a consequence of its rapid metabolism. Appropriate photoperiodic response is indeed obtained when melatonin is administered via a similar subcutaneous infusion system with a dose that mimics the endogenous secretion profile.<sup>15,76</sup> Most likely, this high dose of melatonin is needed because it is an integral part of the response observed. *In vitro* administration of melatonin can phase shift the firing rate of SCN neuron brain slices (rat and mouse).<sup>77,78</sup> It is principally for this reason that it is generally believed that melatonin mediates these effects through the high-affinity melatonin receptors located within the SCN.<sup>61,79</sup> The high correlation between the density of melatonin receptors within the SCN and the ability of daily melatonin administration to entrain the free-running activity rhythm in mammals supports this view. In contrast to the rat, mouse, and Djungarian hamster (rodents that can be entrained by daily melatonin administration and in which a high density of melatonin receptors is observed within the SCN), the mink (*Mustela vison*) does not appear to have specific melatonin receptors (at least 2-iodomelatonin binding sites) within the SCN. This animal does not entrain to melatonin.<sup>80</sup> Newborn Syrian hamsters express

melatonin receptors in the SCN, but the receptor number decreases shortly after birth.<sup>81,82</sup> Young hamsters are entrainable by daily acute melatonin administration, while, in the adult, melatonin is unable to entrain<sup>83,84</sup> or synchronize, except under particular experimental conditions (eg, long-term infusions which affect the  $\tau$ ).<sup>70,72</sup> Since SCN-lesioned hamsters whose rhythmicity had been restored with fetal hypothalamic graft are entrained by daily melatonin injection, it is evident that the chronobiotic effect of exogenous melatonin is the consequence of an action on the clock. This conclusion is supported by the observation that *in vivo* a melatonin receptor antagonist (S 22153) blocks the phase-advancing effect of melatonin.<sup>85</sup>

Which receptor subtypes are involved? Siberian hamsters without a functional MT2 receptor show circadian responses to melatonin.<sup>86</sup> Similarly, the most robust entraining response to melatonin, synchronization of developing circadian pacemakers in Syrian hamsters by melatonin injections, occurs in the absence of a functional MT2 receptor within the SCN.<sup>87</sup> This strongly suggests the implication of MT1 receptors. In *in vitro* experiments in animal models that possess both subtypes, the mechanisms involved appear to be more complex. An acute inhibitory effect on neuronal firing and a phase-shifting effect in the rhythm in electrical activity have been described.<sup>88</sup> In mice with a targeted deletion of the MT1 receptor, the acute inhibitory effect of melatonin was abolished, while the phase-shifting effect remained intact.<sup>88</sup> However, this phase shift disappears when the MT2 antagonist 4-phenylpropionamidotetraline (4P-PDOT) is added.<sup>89</sup> This suggests that either a low density of MT2 receptors is still capable of producing a phase shift or that an as yet unidentified melatonin receptor subtype is involved. In contrast to previous studies, van den Top et al<sup>90</sup> have recently demonstrated the absence of a specific window of sensitivity for melatonin to inhibit SCN neuronal activity. This lack of a window of sensitivity contrasts with the phase-shifting effect of melatonin, and indicates that the cellular mechanisms involved in the acute inhibitory effect and in the phase-shifting effect of melatonin are distinct. This may be related to the two types of effects observed *in vivo* after daily 8 or 16 h melatonin perfusions<sup>69</sup> described above.

The presence of MT1 and/or MT2 melatonin receptors appears to be a necessary condition for the chronobiotic effect of melatonin. However, if these high-affinity melatonin receptors were the only mechanism involved, it

would be difficult to explain why a pharmacological dose of melatonin is needed. This implies that other neural mechanisms may be involved. Although a strong modulatory role of exogenous melatonin on serotonin (5-hydroxytryptamine) 5-HT receptor-mediated responses has been reported, the 5-HT system does not appear to be crucial to the effects of melatonin on circadian rhythms.<sup>91</sup>

### Conclusions and perspectives

Melatonin is produced nocturnally by the pineal gland, in a pattern that reflects the phase and duration of the night. The physiological roles of the hormone directly relate to the temporal information it conveys. In fact, nocturnal melatonin secretion is a hormonal output signal of the circadian clock able to convey photoperiodic as well as circadian signals to multiple structures and organs possessing melatonin receptors, within the brain or at the periphery. This explains why melatonin appears to act in so many different systems.

The use of melatonin to control seasonally expressed traits of economic importance (milk and wood produc-

tion, etc) in farm animals is now well documented, and the sites and mechanisms of action involved are beginning to be identified. The exact role of the hormone in the circadian timing system remains to be determined. However, due to the presence of melatonin receptors within the SCN itself, exogenous melatonin has been shown to affect the circadian clock in animal models (chronobiotic effect). The observations that, in humans, melatonin improves some circadian-based disorders refer to such properties and will lead to strategies to treat, prevent, or delay such disturbances. Melatonin, as explained above, acts through several mechanisms. The hormone's physiological functions—and thereby its therapeutic potential—will depend on our knowledge of its mechanism of action. Today, the pathways through which temporal information encoded in the melatonin signal is decoded in target tissues, and the phenotypic nature of those target tissues, are not completely understood. Experimental work in animal models is still needed to define exactly the therapeutic value of the hormone (for more perspectives with the use of pharmacological tools based on melatonin receptors and  $\alpha$ -antagonists see reviews in references 63 and 92). □

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# Basic research

## Melatonina en modelos animales

La melatonina es una hormona que es sintetizada y secretada durante la noche por la glándula pineal. Su producción es controlada principalmente por el reloj circadiano, el cual en los mamíferos está situado en el núcleo supraquiasmático del hipotálamo. La producción y liberación de melatonina tiene perfiles de secreción característicos tanto diarios (nocturnos) como estacionales (cambios en la duración proporcional a la duración de la noche). Estos ritmos en la melatonina circulante son fuertes sincronizadores para la expresión de numerosos procesos fisiológicos. En los mamíferos, el papel de la melatonina en el control de la estacionalidad está bien documentado, y los sitios y mecanismos de acción involucrados se están comenzando a identificar. El papel exacto de la hormona en el sistema de ritmo diurno (circadiano) debe ser determinado. Sin embargo, se ha observado que la melatonina exógena afecta el reloj circadiano. Los mecanismos moleculares y celulares que participan en este efecto "cronobiótico" bien caracterizado también han comenzado a ser identificados. El reloj circadiano en sí mismo parece ser un sitio importante para el efecto de arrastre de melatonina y la presencia de receptores de melatonina parece ser un prerrequisito. Una mejor comprensión de tales efectos "cronobióticos" de la melatonina permitirá aclarar el papel de la melatonina endógena en la organización circadiana.

## Mélatonine et modèles animaux

La mélatonine est une hormone synthétisée et sécrétée par la glande pinéale. Cette synthèse est sous le contrôle de l'horloge circadienne localisée chez les mammifères dans les noyaux supraquiasmatiques de l'hypothalamus. La sécrétion de mélatonine est nocturne (caractère journalier) et la durée de cette sécrétion est proportionnelle à la durée de la nuit (caractère saisonnier). Ces variations rythmiques de la sécrétion de mélatonine permettent de distribuer à l'organisme un message journalier et saisonnier. Chez les mammifères, le rôle de la mélatonine dans le contrôle des fonctions saisonnières est maintenant bien démontré et les sites et mécanismes d'action commencent à être bien identifiés. Le rôle exact de la mélatonine dans l'organisation journalière des fonctions reste à déterminer. Toutefois des administrations de mélatonine exogène sont connues pour agir sur le système circadien. Les mécanismes moléculaire et cellulaire impliqués dans cet effet « chronobiotique » de l'hormone commencent à être identifiés. L'horloge circadienne elle-même semble être la cible principale et la présence de récepteurs à la mélatonine est nécessaire. Déterminer ces mécanismes d'action permettra de clarifier le rôle de la mélatonine endogène dans l'organisation circadienne des fonctions.

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